

1 ratios of chromium levels in red blood cells to plasma
2 is so different that both blood compartments need to
3 be evaluated, and that was a very valid statement. In
4 fact, it is intracellular chromium that tends to be
5 more of a health hazard than the extra cellular
6 chromium.

7 Can I have the next slide, please?

8 So we looked at a group of nearly 260
9 patients, and we did simultaneously seat them and hold
10 the balances, and when we look at their results, we
11 find that this is normalized scatter in which the
12 whole blood level has been brought to one by adding a
13 correction factor, and the same correction factor was
14 applied to the serum levels are allowed to scatter as
15 they correct the whole level.

16 So this scatter shows that at the lower
17 concentrations, the variability between whole blood
18 and serum is much more ^o than at the higher
19 concentrations. So they are starting with, say, a
20 little lower concentration and then going on to a
21 patient bilateral that's much higher. We're not
22 exactly sure whether the serum level is representing

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1 everything that is contained in whole blood as a whole
2 or not.

3 So there is a larger element of
4 variability at lower levels.

5 Can I have the next slide, please?

6 And the same thing is also seen by the
7 Pearson correlation coefficient. In the first graph,
8 the whole blood levels for below one microgram per
9 liter, and you find that the correlation coefficient
10 is very low, not .14 as compared to over two where the
11 correlation seems to be very good.

12 Can I have the next slide, please?

13 We also tested it with another statistical
14 method that was just called a Bland Altman plot, and
15 we find that the limits of agreement between whole
16 blood and serum are too far apart to give us
17 confidence that serum is able to predict lively what
18 is contained in whole blood, and we believe whole
19 blood is a measure of the systemic metal ions exposure
20 or the body burden of metal ions as a whole.

21 Thank you.

22 PANEL CHAIRPERSON NAIDU: Thank you.

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1 I do have a question for you, but
2 nevertheless, you still have not answered the
3 question. Dr. Mayor stated that it went up more than
4 double for bilateral, and you did admit that, didn't
5 you?

6 DR. DANIEL: Yes.

7 PANEL CHAIRPERSON NAIDU: So it did go up
8 no matter how you measure it, whether it be in the
9 serum or whole blood. After the bilateral
10 arthroplasty, correct me if I'm wrong, but it did more
11 than double, at times triple, correct?

12 MR. DANIEL: No, it didn't go up to
13 triple. The daily output went up to triple or the
14 urinary excretion of metal ions went up three times,
15 but the whole blood levels did not go up to three
16 times, and the daily output -- the fact that whole
17 blood does not increase as much in terms of factors as
18 urine seems to suggest that the kidneys still have a
19 threshold to take in more chromium and get rid of it.

20 PANEL CHAIRPERSON NAIDU: Thank you.

21 DR. MAYOR: One final question and then
22 I'll yield. For the company is there a formal design

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1 for a revision system that would assure that the
2 conversion from a surface replacement to a total hip
3 stemmed implant would produce a good match between the
4 head and the cup.

5 MR. BAND: Tim Band, Smith & Nephew.

6 There was actually a revision system for
7 this component for the femoral side, which is a
8 modular head. It has produced the same exacting
9 standards and specifications material both in terms of
10 microstructure, sphericity and so on and has a taper
11 which is compatible with all of the Smith & Nephew 12-
12 14 tapered stems. So there's a full modular system.

13 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
14 Mayor.

15 We'll come back to Dr. Blumenstein when we
16 deal with the statistics in more detail. I'd like to
17 get the clinical reviewer's comments over with at this
18 point. I'd like to go to Dr. Skinner.

19 DR. SKINNER: Me first? Okay. This is
20 Dr. Skinner.

21 I'd like to ask a couple of questions.
22 I'd like to follow up on the renal function thing.

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1 the thing that worried me from the data that I saw was
2 that for a patient who would walk two million cycles a
3 year -- and we're talking active, young patients --
4 looking at the wear data for the steady state, it
5 looked to me like walking two million cycles per year
6 would give you about a steady state disposal of the
7 cobalt and chromium that you get into your blood by
8 the kidneys.

9 But if you walked more than that, you
10 would have to boost up the excretion in the kidneys to
11 keep the mass balance from shifting to a higher level
12 that would mean you'd be accumulating cobalt chromium.

13 You didn't address cobalt. It sounds like
14 chromium would take care of itself, but it also raises
15 a question that perhaps this should be contraindicated
16 in people who are likely to have renal failure, for
17 instance, in diabetes. Could the company or one of
18 the physicians comment on that?

19 MR. DANIEL: This is Joseph Daniel again
20 from Birmingham in England.

21 The first question about cobalt and
22 activity, cobalt levels and activity, we did a study

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1 looking at output versus activity as measured by step
2 activity monitor, and we did not find any correlation
3 between activity and the cobalt or the chromium
4 levels. We did the same thing against age and against
5 body weight, and a product of activity and body
6 weight, and we did not find any correlation.

7 In fact, Dr. Josh Jacobs, again, has done
8 another study in which he subjected patients to
9 rigorous activity like treadmill walk. You did the
10 serum levels before the activity.

11 If I can have a minute, I'll just show
12 you.

13 I'm sorry. I'm unable to find that, but
14 he concluded in that study that activity and serum
15 metal ion levels do not show any correlation. In
16 fact, he did not find any increase at all when he
17 measured the serum metal ion levels before the
18 activity, during the activity, after the activity, and
19 a time period a few days after the activity as well.

20 I might be able to show that slide if I
21 can have a few minutes.

22 DR. SKINNER: I think that would be okay.

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1 I was concerned because, of course, an accumulation
2 of cobalt might be a problem based on those
3 cardiomyopathies that were associated with high cobalt
4 doses years and years ago in the literature. We
5 certainly don't want to get into a situation like
6 that.

7 MR. VELEZ-DURAN: Marcos Velez from Smith
8 & Nephew again.

9 In the presentation of labeling, we are
10 planning to contraindicate this product for patients
11 with borderline renal failures.

12 DR. SKINNER: Well, there's a very high
13 percentage of people with diabetes or will have
14 diabetes, which means they'll have probably
15 hypertension, and then they'll have renal problems.
16 I'm asking is diabetes something that ought to be
17 considered in there.

18 MR. VELEZ-DURAN: Actually we did not
19 consider that, but we'll take it under advice, and
20 we'll discuss that with FDA as well.

21 DR. SKINNER: Going to another question,
22 Dr. McMinn, Mr. McMinn did this procedure according to

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1 a protocol that was given with a rather sizable
2 incision, and it looks like to get the exposure you
3 need to do the cup and keep the femoral head on, but
4 it's going to be difficult to do with something that's
5 very popular in the States now, the mini incision.

6 Should the labeling perhaps mention
7 something about relatively contraindicated for a mini
8 incision?

9 DR. McMinn: Derek McMinn, again.

10 I'm not sure that would be required. I've
11 been doing mini incision resurfacing for some years.
12 So, for example, we've looked at all the cases that
13 I've done through 2004, and the mean incision length
14 was 11.6, I believe, centimeters.

15 So it can perfectly well be done through a
16 small incision if the surgeon wants to do that. We
17 have looked at a load of objective measures, blood
18 loss, length of time in hospital, and we find no
19 correlation between incision length and the objective
20 data that we have recorded.

21 So from a surgeon point of view, there
22 really is not a very pressing reason to go to mini

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1 incision resurfacing.

2 We have got a group of over 40 patients,
3 however, who have had a standard incision resurfacing
4 in the past, and more recently have had a smaller
5 incision, and we took the opportunity to ask those
6 patients what they felt, and unlike our objectively
7 collected data or at least what we thought was
8 objective data, blood loss, et cetera, the patients
9 almost uniformly preferred the short incision.

10 So there will be surgeons who want to go
11 to a short incision, but it is technically more
12 difficult, and when I take surgeons through their
13 early procedures, I strongly advise them not to go
14 with a small incision surgery and make life even more
15 awkward for themselves.

16 So we have started surgeons in 23
17 countries. So we know quite a lot about how to get
18 surgeons going safely with the Birmingham hip
19 resurfacing, and the one thing I would urge them not
20 to do is to try mini incision surgery.

21 When they're really proficient at the
22 operation, if they do desire and their patients so

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1 desire, then they can reduce the length of the
2 incision. But since it's not a big deal in terms of
3 outcome, objectively assessed outcome, not a good
4 reason to start there.

5 Does that answer you questions?

6 DR. SKINNER: It certainly does. I didn't
7 know you had done them through the mini incision.

8 No questions.

9 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
10 Skinner.

11 Mr. Whittington.

12 MR. VELEZ-DURAN: We have somebody else
13 that can offer a different point of view on the
14 incision size from the U.S.

15 DR. ROGERSON: Dr. John Rogerson from
16 Madison, Wisconsin.

17 Again, I've not put in a lot of these, but
18 I've sent 30 patients to Europe, and the thing that
19 has been impressive to me is that these patients have
20 come back from Dr. DeSmith with large incisions, and
21 yet have qualitative differences in terms of less pain
22 with those bigger incisions than the ones that I'm

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1 doing with mini invasive approach.

2 And I think that that speaks to pain
3 generation in total joint arthroplasty, and I don't
4 know that the pain generation is all related to the
5 size of the exposure. I think that my experience with
6 the Coffield shoulder resurfacing arthroplasty is that
7 those patients have much less pain than a traditional
8 hemiarthroplasty or one that's stem, and the people
9 that I see that have had resurfacing arthroplasty in
10 the hip really don't have much pain with the procedure
11 even though the incisions and the exposure are
12 considerably greater.

13 So I have been impressed that the pain
14 related to the -- and I guess the final thing I would
15 say is the patients that come in, and you know, I will
16 tell them you're going to have a longer incision if
17 you have this operation -- they have all done their
18 homework. They've been on the Internet. They know
19 exactly what the incisions are involved. What they're
20 interested in is not minimally invasive skin
21 incisions. They're interested in minimally invasive
22 surgery and what their long-term prospects are for a

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1 conservative resurfacing replacement, but more
2 particularly for revision later than just the fact
3 that it's a small incision.

4 They're not at all interested or even
5 really care about the size of the size of the
6 incision. They'll tell you that right up front. They
7 really want to continue with an active life style and
8 then when it comes time for revision later to have
9 that be a more conservative operation.

10 PANEL CHAIRPERSON NAIDU: Thank you.

11 MS. WHITTINGTON: My questions related to
12 patient safety specifically as the consumer
13 representative on this panel. I'm concerned about the
14 patient labeling information that would indicate to
15 the community reader, to the typical patient
16 population. Renal insufficiency I don't think means a
17 whole lot to them, and I think the previous question
18 on long-term effect on the potentially chronic kidney
19 disease patient, what kind of methods do you have in
20 place to screen patients or is there a proposal to
21 screen patients for the level of kidney disease and
22 have you identified those patients in which this would

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1 be contraindicated because of the level of kidney
2 disease?

3 Similarly, the same type of question for
4 the patient with avascular necrosis. In my practice,
5 my experience those patients surf the net
6 dramatically, and they're very aware of the procedures
7 that are available, and yet it simply says avascular
8 necrosis, and yet there is a specific level of tissue
9 death or damage to the femoral head that you've
10 identified that you wouldn't progress to.

11 And yet that, indeed, is where as
12 previously asked about the femoral neck fractures, and
13 it's a higher incidence in this patient population,
14 and the inability to differentiate or really decide
15 between avascular necrosis and femoral head collapse.

16 So I'm concerned that these younger, more
17 active people are not going to understand why they
18 can't have this. I think it needs to be clearly
19 identified. I don't see that identification or that
20 description in your patient labeling information that
21 you submitted with the materials.

22 MR. VELEZ-DURAN: These are good points

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1 that you have brought up, and our proposal would be to
2 work with FDA to consider those concerns and reflect
3 them in our labeling. And if there's anybody from
4 Smith & Nephew that would like to add something,
5 they're welcome.

6 DR. McMINN: Derek McMinn again.

7 Please have in mind that my main patient
8 age at operation is 53, and so it's rare in a fit
9 individual of 53 to find significant renal problems.
10 I think the issue of renal insufficiency with metal-
11 metal bearings is going to be much more important in
12 the metal-metal total hips, which will get done on a
13 much older group of patients, and they will be done
14 because of the large head to reduce the chances of
15 dislocation, but the resurfacing group, they're
16 generally fitter and they don't have renal problems,
17 in general.

18 Does that address some of your concerns at
19 least?

20 MS. WHITTINGTON: It doesn't address just
21 a screening, you know, a GFR or a creatinine on
22 patients. In my experience I see more people than I'd

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1 like to see with chronic kidney disease that are not
2 aware that they have it.

3 So asking a patient history is not going
4 to give you the information, especially given the
5 incidence of increased metal ions and the potential
6 problems with that.

7 DR. McMINN: All of our patients have
8 creatinine and urea preop. If they're abnormal, they
9 don't have a metal-metal bearing.

10 MR. VELEZ-DURAN: Once again, the comments
11 are well taken, and we will work with FDA on the
12 specifics of the labeling.

13 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
14 Whittington.

15 Ms. Adams.

16 MS. ADAMS: Just as a follow-up to that
17 question regarding labeling, I want to clarify the
18 labeling that we're looking at is the labeling that
19 the sponsor has submitted which would be part of the
20 prescription labeling that the physician would see.
21 Is it intended that this is the labeling that would be
22 used for consumers if someone were to go to the Smith

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1 & Nephew Web site, for instance, to read about this?

2 MR. VELEZ-DURAN: There will be specific
3 patient labeling that would be developed.

4 MS. ADAMS: So when you say you would work
5 with the FDA to consider these concerns, it would be
6 in the context of the patient labeling?

7 MR. VELEZ-DURAN: Correct.

8 MS. ADAMS: Okay. Thank you.

9 MR. VELEZ-DURAN: Thank you for the
10 clarification.

11 MS. ADAMS: I have another question, which
12 is really I'd like to ask the sponsor to return to
13 some of the questions that were asked earlier. There
14 were two questions that were asked regarding deaths
15 and wanting a little bit more information about
16 patient deaths in the study, and then there was also a
17 question by Ms. Whittington having to do with whether
18 there was a correlation of infections to revisions.

19 MR. VELEZ-DURAN: Thank you for bringing
20 those. We did promise we would look into that
21 particular information and bring it back so the
22 opportunities for us to respond.

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1 Ms. Marlow has put together a summary of
2 that information based on the data that was provided
3 on the PMA.

4 MS. MARLOW: Marie Marlow.

5 Pam, thank you for giving us the
6 opportunity to provide these responses. During the
7 break we were able to do these additional analyses for
8 you. As far as the deaths go, we're going to get a
9 table up here for you. We stratified them according
10 to age. It turns out that the average age of the
11 patients who died was 63 at the time of death.

12 For example, the youngest patient, I
13 believe that age is 53, but we'll have that for you up
14 here in just a moment, died of suicide. There are
15 several cancer deaths in this patient population.

16 All right. So here's the summary of the
17 causes of death, and again, the range in age there, of
18 course, is the time at death.

19 Is the table available? Great. Thank
20 you.

21 All right, and then there's the breakdown
22 for you. Age at the time of death and cause of death,

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1 and we've stratified this table for you by age at the
2 time of death, and if I can provide any more
3 information than this just ask, and hopefully I'll be
4 able to do so for you.

5 MS. ADAMS: If I could ask a follow-up
6 question, how you determined that there have been any
7 deaths associated with this device?

8 MS. MARLOW: No, there's been no deaths
9 whatsoever associated with the device or the
10 procedure.

11 MS. ADAMS: Thank you.

12 MS. MARLOW: All right, and then I'll turn
13 the second question over to George DeMuth who took
14 some of the data on the infections and the wound
15 exudates for you.

16 MR. DeMUTH: Yes, I may have to refer to
17 somebody else as well.

18 The first cut was just to look at whether
19 the revision rate at all was hiring patients that had
20 wound accident. Just in a percentage basis, it was
21 four out of the 589, you know, .7 percent essentially,
22 and out of the remaining patients were the 23 other

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1 revisions, 1.3 percent. So more revisions in the
2 patients that didn't have wound exudate.

3 Then when you go look at specific due to
4 infection, only one of the four in the wound exudate
5 patients was related. So it's 0.2 percent of the
6 patients. These aren't survival rates. They're just
7 cut rates. The other seven were actually in the non-
8 wound exudate patients and so, again, 0.4 percent. So
9 it didn't appear to be at that kind of gross look
10 associated with it.

11 MS. ADAMS: Thank you.

12 I'd also like to ask some questions and
13 make a comment regarding financial disclosure and
14 conflict of interest. The panel received three
15 letters that are, to my knowledge, intended to be part
16 of the record, but there was no information regarding
17 conflict of interest associated with the letters. I
18 just want to clarify whether or not we have received
19 any of that information.

20 MS. SCUDIERO: The letters are just since
21 we received them. There was nothing -- the people who
22 sent the letters received that same little statement

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1 that I provided to all the other speakers about
2 conflict of interest, and it says that you don't need
3 or you don't have to state your position or if you
4 have any affiliation you can still submit or still
5 speak, and I think it was probably just overlooked.

6 MS. ADAMS: Thank you.

7 Also I'd like to come back to the comments
8 that were made during the public session. The
9 distinguished Dr. Maloney made some comments regarding
10 financial interest. I know we as a panel because we
11 received training on this are not supposed to consider
12 those, and that that's not the subject of our
13 deliberations today, and given that, I would like to
14 also just acknowledge that it is, of course -- there's
15 probably no panel that ever meets that doesn't have a
16 significant amount of financial impacts that will come
17 from our deliberations, and even though we're not
18 going to talk about them, I don't think there's
19 anything unusual associated with that sort of thing,
20 especially with devices that are presented to our
21 panel which represent new technology such as this.

22 Nevertheless I do want to ask the sponsor

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1 whether or not they have met their regulatory
2 obligations regarding disclosure in the PMA having to
3 do with finances and conflict of interest.

4 MR. VELEZ-DURAN: The appropriate
5 financial disclosure materials have been submitted to
6 PMA as required and FDA has at least part of our PMA.
7 If FDA wants to comment on that they're welcome to.

8 MS. ADAMS: Thank you.

9 PANEL CHAIRPERSON NAIDU: No comment?

10 MR. MELKERSON: The financial requirements
11 are actually part of filing. If that information is
12 not there, the PMA would not be. It's the one reason
13 for not filing a PMA.

14 PANEL CHAIRPERSON NAIDU: Thank you, Mr.
15 Melkerson.

16 MS. ADAMS: Thank you.

17 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
18 Adams.

19 Let's continue with the clinical
20 discussion. Dr. Kim.

21 DR. KIM: Hi. Choll Kim from UCSD.

22 I have a couple of questions. Let me just

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1 start out with one at a time.

2 There's been some mention that the surgery
3 can be challenging technically, but we didn't hear
4 much about any analysis of a learning curve. Do you
5 have any information or data that would give us a
6 better idea of this learning curve and how many cases
7 one would expect to have to do to be at a level where
8 we can do the surgery reliably?

9 MR. RORABECK: All right. Cecil Rorabeck
10 again.

11 That's a key question, and I'm sure to
12 some extent it's going to vary from surgeon to
13 surgeon, but let me just say this. As someone who is
14 doing the technique and somebody who has spent my life
15 basically doing hip and knee surgery, first of all, I
16 don't think people should be turned loose with a
17 technique like this until they've had appropriate
18 training, and in our country we have workshops where
19 they come and actually do a cadaveric lab to learn the
20 technique, and I think in my opinion that's a good
21 thing to do.

22 Having said that, I think to get up to

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1 speed with this, one first has to see somebody do the
2 technique and probably see two or three cases, follow
3 a video, do the sawbones, and so on, and at the end of
4 that, assuming the person is going, say, 50 hips a
5 year, I would think that the learning curve is going
6 to be about ten to get up to a level of comfort.

7 And why do I say that? Well, I think that
8 I'm talking about picking and choosing patients
9 carefully, and if we pick men under the age of 60 that
10 are not particularly obese or women with normal DEXA
11 scans, again, 60 or less, I think we're going to learn
12 pretty quickly.

13 On the other hand, if we're picking people
14 that are 68 that are obese and various things, it's
15 going to be more complex.

16 DR. KIM: I take it from your answer
17 though that there is no data that we can evaluate to
18 get a handle on this.

19 DR. RORABECK: Well, you're quite right.
20 There is no data.

21 DR. KIM: The second question has to do
22 with bone stock. Is there a quantitative value that

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1 was identified to help us figure out which patient has
2 adequate bone stock and which one does not?

3 DR. RORABECK: Well, as I've said, I think
4 that a DEXA scan is important in women in particular.

5 In men we evaluate them the same way as evaluate a
6 patient for a cementless total hip replacement. If
7 they've got appropriate bone stock in terms of a Type
8 A or B bone, then they're probably going to be a
9 candidate for resurfacing.

10 So in that sense we use a similar
11 indication.

12 DR. KIM: One final question has to do
13 with the metal ion discussion. I haven't had a chance
14 to review this data and unfortunately the PMA does not
15 do a very good job of explaining to us at what value
16 having metal ions is detrimental to our health. It
17 doesn't even talk about animal data. So is there --
18 do you know of any data or anyone in the sponsor group
19 have some information that would reassure us that the
20 metal ion concentrations that we're seeing are
21 detrimental, safe? How far from detrimental are they?
22 What orders of magnitude below those thresholds are

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1 they? Questions like that.

2 DR. RORABECK: I think one of the things
3 that has been most interesting to our group, and we
4 did a prospective randomized trial looking at metal-
5 metal versus metal on polyethylene in a group of
6 patients blinded as to which hip they had, and that
7 data is now out five years. Our metal ion levels, and
8 these are intracellular, cobalt and chromium ion
9 levels and the metal-metal group are clearly higher.

10 And while they're higher in year one and
11 two, there is a tendency for them to fall off toward
12 year five, but what's the significance of these data
13 and what does that really mean?

14 And our data is not dissimilar from the
15 data that's in your handout.

16 I think that we've looked at it as
17 carefully as we can, and what we've done is we've gone
18 to the various governments around the world like the
19 British government, Canadian government, the German
20 Ministry of Labor to find out when somebody would be
21 taken off an assembly line with a serum cobalt of X,
22 and that's the yard stick or the meter stick that

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1 we've been using in our country to try and define
2 what's acceptable and what isn't because you're quite
3 right. We do not know the answer to this.

4 And I can assure the panel that with no
5 exceptions in our data and I think also in this data,
6 the serum ion levels fall within acceptable levels of
7 the Entero (phonetic) Ministry of Labor or the German
8 Ministry of Labor or the U.K. Ministry of Labor.

9 Now, I could not get data for the U.S. on
10 that, but that would be my answer to it. We don't
11 know the answer, but I think we're acceptable.

12 DR. KIM: Thank you.

13 MR. VELEZ-DURAN: I just wanted to follow
14 up to the response. You're correct that we do not
15 have a specific analysis of learning curve. However,
16 we do have significant numbers of series of patients
17 that have been performed over the years. The
18 survivorship percentages are very high, not just for
19 Mr. McMinn, but published series in the British
20 Journal of Bone and Joint, as well as the experience
21 in the Oswestry Center for a total of about 140 other
22 surgeons.

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1 So still the survivorship is very, very
2 good at five years for those patients. So just to
3 give you a level of confidence on that.

4 And there may be some additional
5 information on ion levels.

6 DR. DANIEL: I'm Joseph Daniel from
7 Birmingham again.

8 Regarding data about the possible adverse
9 effects on health due to metal ions, there are two
10 main concerns which seem to come up from time to time.

11 One is what does it do in terms of cancer rates, and
12 two is what happens in children and women of child
13 bearing age whether they crossed the placenta or not.

14 So in holding on to these two questions,
15 there is one reference by Visuri from Finland which
16 was submitted along with the PMA, which talks about
17 cancer rates in patients with metal-metal total hip
18 replacements.

19 Can I have the slide, please?

20 Visuri followed up a series of 579
21 historic metal-metal total hip replacements done from
22 1967 and followed them up for a 30-year period. The

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1 28-year results are shown here. He has shown that
2 when compared to the general population there is no
3 difference either in the all site cancer rate -- next
4 one, please -- or in the site specific cancer rate,
5 and the only difference is in lung cancer in which if
6 you see the 95 percent confidence intervals both the
7 limits are less than one.

8 So lung cancer is lower in incidence as
9 compared to the general population, and in the rest of
10 the site specific cancer rates, all of the 95 percent
11 confidence intervals cross one, which means there is
12 no significant difference between this group and the
13 general population. The total number of person-years
14 considered in this is 9,700 and on, and this compared
15 very well with the metal-on-polyethylene total hip
16 replacements as well, which was studied in other
17 studies, a series of analysis of 70,000 patients also
18 shows similar results and there is no difference.

19 On the question of whether it affects the
20 unborn child -- can I have the next slide, please? --
21 there is only one publication at present, and this
22 seems to suggest -- the next one, please -- that the

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1 blood serum metal ion levels are not recordable in
2 umbilical cord blood in patients with metal-metal
3 hips.

4 DR. KIM: Thank you.

5 Are we going on to discussion of the
6 statistics?

7 PANEL CHAIRPERSON NAIDU: Let's just
8 finish with Dr. Mabrey, and then we'll go into
9 statistics.

10 DR. MABREY: I had three questions. Two
11 of them are primarily for clarification.

12 Number one, I'd like to just clarify that
13 100 percent of all of the acetabular cups evaluated
14 with the Oswestry study were HA coated throughout from
15 the very beginning of the study.

16 MR. BAND: Tim Band, Smith & Nephew.

17 All of the components were HA coated.
18 There's been no design changes to the system.

19 DR. MABREY: And no change in the
20 technique of application of HA.

21 MR. BAND: No.

22 DR. MABREY: Second, what percentage of

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1 cases does the sponsor anticipate would require use of
2 the dysplastic cups?

3 This application is slightly different in
4 that we're not just looking at one acetabular system,
5 but actually three, the acetabular cup and the
6 bridging cup as well as the standard cup.

7 I do remember some numbers from Mr.
8 McMinn's study, but his population may not necessarily
9 reflect the number of acetabular or dysplastic cases
10 out there.

11 DR. McMINN: Derek McMinn again from
12 Birmingham.

13 In my series of Birminghams, I had 176
14 dysplasia cups out of, I believe, 2,300. So somebody
15 mentioned a figure of seven percent, if anybody is any
16 good at math.

17 However, that very much depends on what
18 you are prepared to take on as a surgeon, and a
19 surgeon who is starting the Birmingham resurfacing
20 would be well advised not to start with a high CDH.
21 That would not be a good place to start, and so the
22 level of usage of the dysplasia system will very much

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1 reflect the experience and confidence of the surgeon.

2 And many surgeons throughout the world
3 using the Birmingham system have a usage of zero.
4 Mine is rather higher than that, but I find it an
5 extremely useful device.

6 Incidentally, in the 176 I had no implant
7 related failures in the 176 dysplasias.

8 DR. MABREY: This gets back to Ms. Adams'
9 comment about the contraindications on the package
10 insert. Now, does the sponsor anticipate adding
11 restriction as to the crow (phonetic) type of
12 dysplasia that one would recommend this for or will
13 that be left to the discretion of the surgeon?

14 DR. McMINN: No, I think you have to leave
15 that to the discretion of the surgeon. Of course,
16 it's very rare that you would ever dream of doing a
17 resurfacing in a crow Rate 4. So you have a tiny
18 acetabulum with a head well up.

19 (A) You don't need a dysplasia cup because
20 that socket is complete even though tiny, and because
21 it's tiny, there's very little prospect of it being
22 able to resurface and get a head that's small enough

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1 onto the head leaving any bone.

2 So fours, I think, for very obvious
3 practical reasons will not be done, but Crowe Rate 3
4 and Crowe Rate 2 are absolutely prime targets for the
5 dysplasia cup. In my practice Crowe Rate 1 often you
6 don't need anything other than a regular spherical
7 cup.

8 DR. MABREY: Thank you.

9 DR. McMINN: Does that answer your
10 question?

11 DR. MABREY: Yes.

12 MR. VELEZ-DURAN: In addition, as you
13 mentioned, it's something that we could consider in
14 labeling, but most importantly we could consider as a
15 factor or something to include in our surgeon
16 training.

17 DR. MABREY: My third question relates to
18 a topic brought up with Dr. Skinner earlier on, and
19 this is the comparison of populations and the
20 percentage of diabetes that one would anticipate.
21 Prior to moving to Dallas, I was situated in San
22 Antonio for 13 years where 50 percent of the

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1 population was of Mexican American heritage.

2 In that particular population of patients
3 and only within the United States they have a much
4 hither incidence, in some cases up to one third of
5 Mexican American Hispanics over the age of 65 have
6 some type of diabetes mellitus.

7 Now, one does not see this in the
8 population in Mexico City. So it happens to be a
9 cultural effect. I bring this up because one of the
10 questions that has been addressed to the panel is are
11 the populations similar, and when I look at the
12 population statistics, I didn't see much comment on
13 the use of this device or follow-up of this device in
14 Hispanics or Mexican Americans.

15 MS. MARLOW: Marie Marlow, again.

16 That's a very good point that any study in
17 the U.S. would have to address is patient
18 demographics, although I wonder with the percentage of
19 Spanish Americans, Mexican Americans in the United
20 States what size of study would have to be undertaken
21 in order, one, to recruit a sufficient population of
22 Mexican Americans, and two, to recruit a sufficient

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1 population of those with diabetes, although this is an
2 excellent consideration.

3 This may be one of the things that we
4 could address in the post approval study by making
5 sure that we select cities where these kinds of
6 representative populations live. That's a very good
7 idea for us.

8 DR. MABREY: That's all.

9 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
10 Mabrey.

11 Let's go on to the statistical discussion.

12 Dr. Blumenstein, if you could start off on that, that
13 would be treat.

14 DR. BLUMENSTEIN: Okay. I just want to go
15 over a couple of things. First of all, from what I
16 can see intervention appears to be effective in some
17 sense and also appears to be reasonably safe given the
18 effectiveness.

19 The issue to me is whether this is well
20 controlled, and by that I mean the effectiveness
21 relative to predicate effective interventions has not
22 been established, and I'm going to go on and explain

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1 that and then make some comments on the fact that this
2 is all limited by the study design.

3 First I want to cover some minor issues
4 that are -- just to get them out of the way. First of
5 all, the estimation of the survivorships are simply
6 wrong, and the reason they're wrong is that the
7 competing risks are either lost to follow-up, but in
8 this case, in particular, death, are censored rather
9 than using a methodology that takes into account the
10 difference between competing risks and limited follow-
11 up, and I can give you references on this if you need
12 to have them.

13 This is a common problem, and it's
14 particularly a problem in things like presentation of
15 Kaplan Meier curves with cause specific deaths
16 censored, deaths not relative to the primary cause.

17 There are substandard data collection
18 practices in this study. There's an unplanned
19 criterion for success. We've already heard these
20 things, and then, of course, there's a single clinical
21 site in another country and a single surgeon which
22 means that you cannot assess the homogeneity of

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1 results across surgeons or site. We just simply do
2 not have that data.

3 What I wanted to address here is the
4 control and cohort studies. No matter what we do when
5 we evaluate an intervention, we're comparing it to
6 something, and there's a specific situation that's
7 important to think about, and that's what's called the
8 unmet medical need, and this is a case where there's
9 no intervention, and you expect either no improvement
10 or worsening relative to the primary efficacy measure
11 if there is no intervention, and there is no existing
12 effective intervention, and this is a situation called
13 unmet medical need, and in that case a cohort study,
14 that is, you call it a case series or if we want to be
15 insulting as statisticians we call it a convenience
16 sample, and so forth. These are appropriate in this
17 unmet medical needs setting because what you're doing
18 is you're trying to see if you can get your measure of
19 effectiveness to show that you do have effectiveness
20 and you have no expectation.

21 But we don't have that situation here, and
22 I wanted to point out that this first in class which

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1 we've heard about here does not refer to the first
2 intervention for this disease. In other words, we do
3 not have in the strictest sense the unmet medical need
4 definition that I gave on the previous slide, and
5 specifically we have effective predicate intervention,
6 and the safety and effectiveness cannot be adequately
7 characterized without comparison to the existing
8 predicate effective interventions.

9 The exception to this is where the
10 predicate would be minimally effective, where you feel
11 that you can, based on the historical data that your
12 result is going to be so overwhelmingly positive
13 compared to some predicate that's only minimally
14 effective, but in general you cannot establish
15 effectiveness when an effective predicate exists.

16 Now, when we compare interventions, the
17 highest standard, of course, is the randomized
18 clinical trial, and that's what I think should have
19 been done here, but what we have here is a single
20 cohort study with a comparison to historical data, and
21 this suffers because the differences in effect, that
22 is, the outcome, are confounded with the cohort

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1 differences, that is, the data that you can use to
2 compare to might have been in a different population
3 or different methods are used to collect the data.
4 Different endpoints are used.

5 We have already seen the score. The
6 differences between the scores have been discussed
7 extensively, and this is further exacerbated when the
8 data that you're comparing to come from literature
9 because you don't have control over the data. You
10 have to accept whatever measures are there.

11 Some people use meta analysis, methodology
12 for comparing interventions, and I just wanted to put
13 up this sort of descending order of validity, and the
14 best kind of meta analysis is when you get the data on
15 all randomized clinical trials, and you put all of the
16 data in a computer and you crunch it.

17 The next level down is where you extract
18 estimate from one or more randomized clinical trials
19 from the literature, that is, you don't have the
20 complete data sets on all of the randomized clinical
21 trials.

22 The next one down is where you get data on

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1 all cohorts and you put it together and crunch the
2 data in a computer.

3 And the last and the least of the methods
4 is extract estimates from one or more cohorts from the
5 literature, and this is exactly the situation that we
6 have here, is that we're comparing a cohort of data
7 from a single institution with a single surgeon, and
8 we're comparing it to literature.

9 And the whole point here is that a meta
10 analysis of randomized clinical trials, there's no
11 confounding of populations to the differences in
12 effect, but just as it would be in any other setting,
13 but the metal analysis of cohorts is still confounded.

14 So there's just no way around that.

15 So for me the bottom line is that the
16 phrase "well controlled" doesn't apply.

17 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
18 Blumenstein.

19 Anybody have any questions for Dr.
20 Blumenstein? Dr. Kim, you had a previous statistical
21 question.

22 DR. KIM: I think you have answered it,

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1 but I just want to make sure I understand. In several
2 of the five-year groups the loss to follow-up
3 percentage is about ten percent. Yet the survivorship
4 is well over 95 percent. If we assume that those ten
5 percent had a high percentage of failures, wouldn't
6 that significantly affect the survivorship analysis,
7 for example, if eight percent out of the ten percent
8 were lost to follow-up because they had a terrible
9 result? Would that affect the final survivorship and
10 if so, by how much?

11 DR. BLUMENSTEIN: Well, the lack of
12 follow-up, if you're estimating survivorship at a
13 particular point in time, say, five years, and not all
14 patients are followed for five years, we have
15 actuarial methods of estimating survivorship based on
16 that, I mentioned that the estimate that's being used
17 is not valid. There are estimates that are valid.
18 The reason the estimate to me is not valid is because
19 deaths which are a terminating event, a competing
20 event, were censored, which is what you do when you
21 have inadequate follow-up on patients.

22 But the lack of complete follow-up on all

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1 patients in and of itself is not a problem. If the
2 lack of complete follow-up is biased in some way, then
3 that's a problem and that has to be dealt with in some
4 fashion.

5 The scores that were analyzed over time,
6 there was some mention about "missingness," whether
7 "missingness" was random or not, and that's going to
8 affect the validity of the statistical analyses, but
9 inadequate follow-up or incomplete follow-up, rather,
10 is in and of itself not necessarily a problem.

11 DR. KIM: Sorry to be so nit picky. If we
12 were to assume that that group of patients did poorly,
13 in other words during the worst case scenario, what
14 would the survivorship value be roughly, in the worst
15 case scenario?

16 Maybe the sponsor can answer that since
17 they may have access to that data.

18 MR. VELEZ-DURAN: Thank you for the
19 opportunity to respond to the questions. I wanted to
20 mention that in the selection of the literature
21 comparison, we actually did a full review of the
22 literature to select the two comparative histories or

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1 literature controls that we selected.

2 It's also worth noting that there are not
3 a lot of randomized clinical studies published on
4 orthopedic devices. So that presents a limitation on
5 any meta analysis that you could perform.

6 I also want to mention that we need to
7 just keep in mind that we only have 27 revisions. So
8 regardless of the method you use to calculate the
9 survivorship, there's only 27 out of a very large
10 cohort.

11 But I would invite our statistician to
12 further comment on the comments by the statistician on
13 the panel.

14 MR. DeMUTH: Well, part of that I'd like
15 to defer, but I think we do know we have 20 patients
16 that died. Without going back and fitting a survivor
17 -- you know, treating those as all failures, for
18 instance to try and maybe to get a bound on death plus
19 revision, we just note, you know, that number of
20 patients or 27 out of the 20 -- I don't know how many
21 of the 1,626. So it seems there's a bound on some, a
22 couple of percent perhaps. Maybe it's a little more,

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1 and so that leads to the possibility that we'll have
2 to defer to what's an appropriate adjustment on that
3 because I think we'd have to go back and estimate to
4 get an accurate or the exact correct estimate if
5 that's the case.

6 If there are other adjustments, I think we
7 kind of have need to know because if that move to
8 survival to three or four percent or adding two
9 percent or one percent, I think it's worthy to know or
10 at least me to know whether that -- it becomes an
11 acceptable rate.

12 There are a couple other comments that I
13 think just in terms of -- well, I'll let it go in
14 terms of potentially.

15 DR. RORABECK: Yeah, this is Cecil
16 Rorabeck, and I just want to talk about your comment
17 about randomized clinical trials because wearing my
18 surgeon scientist hat -- and this is something we've
19 been involved in for many, many years during
20 randomized clinical trials of new surgical technology
21 at our university, and we started initially doing
22 cementless hips and with prospective blinded trials.

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1 They probably have here, and I'm not
2 apologizing for the data. The data is what the data
3 is, but from a practical standpoint, and we have the
4 same problem today doing this particular thing in our
5 country, is that people are coming asking specifically
6 for this procedure, and it's very hard to enter them.

7 We currently have a randomized clinical
8 trial going now comparing Birmingham to synergy Big
9 Head Birmingham come, randomized, prospective, blinded
10 trial, but the vast majority of our patients come
11 because they want to have a Birmingham hip
12 replacement.

13 So, you know, you get into ethical issues
14 and other issues, and I don't disagree with your
15 comment. That certainly is the gold standard.
16 Whether it's generalizable to all devices is another
17 issue entirely, but it's difficult for us to be able
18 to do this even though we're trying.

19 PANEL CHAIRPERSON NAIDU: Yes, Dr.
20 Skinner.

21 DR. SKINNER: I'd like to ask Dr.
22 Blumenstein or the statistician for Smith & Nephew.

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1 It would seem to me that if a patient dies, he's no
2 longer at risk for a revision. So that would tend to
3 make the survivorship better. Is that wrong?

4 DR. BLUMENSTEIN: Exactly.

5 MR. DeMUTH: I think what it is is you've
6 lost the potential that you're not going to catch an
7 event.

8 DR. SKINNER: So that would only make the
9 data look better. Well, I mean, I think the point is
10 that if you want to say we've lost potentially 27
11 potential events because a patient has died, then we
12 may have some bias going the wrong direction in
13 favoring the device as opposed to, say, the worst
14 case, which maybe you treat them all as failures.

15 I feel like the truth is probably
16 somewhere in between

17 DR. BLUMENSTEIN: Yeah. I mean, the issue
18 is that it's just the wrong methodology to estimate
19 survivorship. It is not going to make a lot of
20 difference in these estimates if you use cumulative
21 incidence, which is the proper methodology in the face
22 of competing risk versus an inverted Kaplan-Meier or

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1 in this case I guess they use just a Kaplan-Meier, but
2 it's just wrong, and you know, maybe I'm tilting at
3 windmills, but it pervades the literature and so
4 forth, and I've just got to say it's wrong every time
5 I see it.

6 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
7 Blumenstein.

8 You've heard that. I think we should
9 proceed by focusing our discussions on the FDA
10 question at this point. Copies of the questions are
11 at the tables outside the room. At this point I would
12 like to ask Mr. Goode to come up and read the first
13 question because there are fairly extensive questions,
14 and we should -- we'll try to go around the room and
15 discuss each question.

16 MR. GOODE: Dr. Naidu, would you like for
17 me to present all the questions or just a single
18 question and then proceed one by one?

19 PANEL CHAIRPERSON NAIDU: I think let's do
20 one by one because these are fairly complex questions.

21 MR. GOODE: Question No. 1, please discuss
22 the evaluation methods used to collect the safety

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1 data.

2 So these are the collection methods used
3 for the safety data, that is, how the data on
4 revisions was collected, adverse events, deaths, and
5 metal ion literature analysis, and whether or not
6 these methods of data collection are reliable to
7 assess the safety of the device.

8 PANEL CHAIRPERSON NAIDU: Thank you, Mr.
9 Goode.

10 Why don't we start with Dr. Mayor.

11 DR. MAYOR: I think we've covered the
12 issue fairly thoroughly in the discussions we've
13 already had, and my response to that would be to
14 suggest that given the FDA's definition of valid
15 evidence, it's valid but certainly far from
16 impeccable.

17 With that observation in mind, I think I
18 would conclude that the methods for collecting safety
19 data are adequate.

20 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
21 Mayor.

22 Dr. Blumenstein?

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1 DR. BLUMENSTEIN: Well, I can't feel good
2 about the way the data have been collected, and in
3 terms of the methods used to extract the data from the
4 records, the lack of prospective design in data
5 collection and so forth. This falls far short of what
6 a study should be.

7 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
8 Blumenstein.

9 Dr. Mabrey.

10 DR. MABREY: I have to echo the sentiments
11 of Dr. Blumenstein that while the data presented is a
12 testament to Mr. McMinn's surgical skills and his
13 clinical practice, much of this represents his data as
14 opposed to that of a much larger group of surgeons.

15 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
16 Mabrey.

17 Dr. Kim.

18 DR. KIM: I would just like to echo the
19 concerns of Dr. Blumenstein and Dr. Mabrey, and I
20 agree with their comments.

21 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
22 Kim.

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1 Dr. Skinner.

2 DR. SKINNER: Well, I have to agree with
3 Dr. Mayor. I think that it's an imperfect world, and
4 it's imperfect data, but I think it's adequate.

5 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
6 Skinner.

7 Ms. Whittington.

8 MS. WHITTINGTON: I would concur with Dr.
9 Blumenstein. I don't think it's adequate, especially
10 in the adverse events and the prediction of potential
11 disasters for patients who might receive this implant.

12 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
13 Whittington.

14 Ms. Adams.

15 MS. ADAMS: Well, I feel a little
16 differently. Being on the side of -- I'm speaking as
17 an industry rep. I'm well aware, even though I don't
18 work with these types of devices, that typically what
19 happens is that 200 patients are studied for a period
20 of one to two years, and based on that, these types of
21 devices are approved.

22 So I have a fair amount of comfort in the

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1 fact that there are thousands of cases here, and
2 there's quite a significant amount of safety data, and
3 although, no, it doesn't follow what we would call the
4 perfect way of doing a clinical trial, which is
5 randomized, controlled, blinded, all those kinds of
6 things, it certainly fits to me within the purview of
7 what the Congress has asked the FDA to do, which is to
8 find the least burdensome way to bring devices to
9 market.

10 The concept in 1997, and I won't bore
11 everybody with it, was that the act was amended so
12 that we could have a least burdensome way. So I will
13 leave it at that and just say that to my way of
14 thinking there is a large amount of data here for us
15 to be able to get some sense of comfort about how it's
16 collected.

17 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
18 Adams.

19 Mr. Melkerson, in regards to Question 1,
20 the panel is, as you heard, generally split. There
21 appears to be equal number of inadequate data
22 positions, and there appears to be equal number that

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1 say that there is valid scientific evidence.

2 And is that adequate?

3 MR. MELKERSON: Being that it is split, as
4 far as adequacy, what would your comments be on this
5 question?

6 PANEL CHAIRPERSON NAIDU: When you look at
7 the valid scientific evidence as defined by the FDA,
8 reports of significant human experience with a
9 marketed device from which it can fairly and
10 responsibly be concluded by qualified experts that
11 there is reasonable assurance of the safety and
12 effectiveness of the device under its conditions of
13 use, in my opinion, there is a large series. There's
14 a large body of data in this study presented. Even
15 though it is retrospective, there have been a few
16 other PMAs that have come up with retrospective data,
17 and we have approved it.

18 And I think there is enough here. There
19 is enough valid scientific evidence. That's my
20 opinion.

21 MR. MELKERSON: And then one follow-up
22 question. We were talking here not necessarily the

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1 quality of the data, but the question of the methods
2 used to collect that data.

3 And I heard one or two comments regarding
4 that it wasn't prospectively designed, and I believe
5 the -- and I ask the sponsor this -- I thought you had
6 proposed ahead of time what that data collection was
7 prior to sending the monitors out.

8 MR. VELEZ-DURAN: Just a couple of
9 clarifications. The first thing is that the Oswestry
10 Center had to get this registry prospectively. So the
11 only thing retrospective was us going back and
12 collecting that information, but prospectively the
13 registry and the method to collect that data were set
14 out prospectively in 1997.

15 The safety data, there was a protocol that
16 was set out for an independent group to collect all of
17 the safety, any adverse event, or any indication in
18 the patient records that there may have been an
19 adverse event. None of those were edited by the
20 person that collected the information.

21 In addition to that, the X-ray evaluation
22 was done independently, and there was a protocol

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1 developed with success and failure criteria
2 prespecified.

3 MR. MELKERSON: I think that's my
4 comments. Thank you.

5 PANEL CHAIRPERSON NAIDU: Have we
6 adequately addressed Question No. 1?

7 MR. MELKERSON: I believe so.

8 PANEL CHAIRPERSON NAIDU: Mr. Goode, could
9 you please pose the second question?

10 MR. GOODE: Question No. 2, please
11 discuss, again, the evaluation methods or the way in
12 which the data is collected for the effectiveness
13 data, that is, the data on survivorship, and if you
14 really again the survivorship in the same way that the
15 safety data was collected was by the Oswestry Outcomes
16 Center and by the McMinn Center.

17 The OSHIP score, which again was a patient
18 self-evaluation of pain and function information, the
19 radiographic information was the zero and five-year
20 evaluation of radiographs on a subset of the patients,
21 as was the patient satisfaction information which,
22 again, was through the mail-in questionnaire.

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1 That's what we're wanting you to comment
2 on, those data collection methods. Comment on whether
3 or not those methods are reliable to assess the
4 effectiveness of this device.

5 PANEL CHAIRPERSON NAIDU: Thank you, Mr.
6 Goode.

7 Why don't we start with Ms. Adams.

8 MS. ADAMS: Well, just one small comment.

9 I just wanted to comment that I liked the patient
10 questionnaire even though I know that there were some
11 felt that maybe that wasn't the best way to go. I
12 think some of the surgeons that implant these devices
13 are very charming, and that when they ask questions of
14 their patients, their patients want to make them
15 happy, and so I think there's a potential for bias
16 when it's a physician administered questionnaire.

17 So just that is a comment. I thought that
18 that was an interesting approach.

19 PANEL CHAIRPERSON NAIDU: Ms. Whittington.

20 MS. WHITTINGTON: I concur with Ms. Adams.

21 In my experience of over 30 years of dealing with
22 orthopedic patients, the best person to ask the

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1 outcome is the patient. So I think that your choice
2 of this method of evaluating the effectiveness needs
3 to be from the patient's perspective because they're
4 the recipient of that.

5 PANEL CHAIRPERSON NAIDU: Dr. Skinner.

6 DR. SKINNER: I also think the data is
7 appropriately collected. My Harris Hip Scores are
8 collected by the MA by asking the patients the same
9 questions, and I think that's the way it's done in
10 most studies. At best you'd have a physical
11 therapist.

12 So I think they were at least equivalent
13 in this particular collection of data to the way it's
14 collected in, say, either of those two ceramic hip
15 studies. So yes.

16 PANEL CHAIRPERSON NAIDU: Thank you.

17 Dr. Kim.

18 DR. KIM: I would agree with the previous
19 panel members that collecting the data from the
20 patient is as important as collecting the data from
21 other objective measures, including physical exam and
22 radiographic findings. So their method of data

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1 collection biasing the patients satisfies that
2 criteria, but I would question the validity of the
3 statement that the data was collected prospectively
4 and retrospectively analyzed since 1997 because if
5 that were the case, I would assume that the data would
6 be collected in a uniform fashion. You wouldn't have
7 three cohorts.

8 So I question the validity of that
9 statement, and that's where I have some significant
10 dilemma in answering this question of the methodology,
11 not the actual contents of the data, but the method by
12 which it was collected I do not agree was appropriate.

13 And in addition, there's some issue -- I'm
14 not a hip surgeon. I'm a spine surgeon -- but there's
15 some issue with the utilization of a relatively
16 uncommon method by which to evaluate patient outcomes,
17 essentially the OSHIP questionnaire, when it seems to
18 me that the Harris Hip Score is the standard in this
19 industry. Correct me if I'm wrong.

20 So there is significant flaws in the
21 methodology in my mind, and we can talk about the
22 actual data in Question 4, but that's my view.

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1 MR. VELEZ-DURAN: If I could just make a
2 few clarifications, and maybe I did not explain the
3 cohorts well.

4 The cohorts were identified simply to
5 identify what group of patients had a specific set of
6 data. They're all part of the 2,385 patients. So in
7 a way, from my perspective, even though we comply with
8 the request by dividing those patients into three
9 cohorts, it's almost an artificial way of looking at
10 these patients. However, that's my opinion.

11 What I would say is that the cohorts, for
12 example, the X-ray cohort and the Oswestry cohort both
13 receive the same questionnaire. So there is no
14 difference in there. The only difference is in the
15 what we call McMinn cohort, which is the most recent
16 cases, and just to explain that a little bit, at the
17 time of introduction of the product, the Oswestry
18 Outcomes Center was commissioned to follow 5,000
19 cases, and all the funding for that was done up front,
20 not based on the result of the registry.

21 At the end, when they collected 5,000
22 cases, which is what we have provided in this PMA,

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1 there was no additional data collected by the Oswestry
2 Center. That's why there is a small group of --
3 there's a group of cases, the most recent, that do not
4 have an OSHIP questionnaire. I just wanted to clarify
5 how that happened.

6 DR. KIM: Well, then I ask the question:
7 if you knew that this was a limited study to test out
8 a new questionnaire system, why not have also, if this
9 was something that you thought up ahead of time, to
10 also include Harris Hip Score and continue that
11 throughout the entire study from 1997 through 2004?

12 MR. VELEZ-DURAN: Yeah, of course, I was
13 not around in 1997 to make that decision, but the
14 Oswestry Center evaluated the Harris Hip Score,
15 evaluated the SF-36, the Womack and other
16 questionnaires, and they decided to develop one that
17 was a patient self-assessment because based on
18 numerous publications the patient self-assessment
19 perhaps is a better assessment of pain and function.

20 And if we want a concise explanation of
21 that at that time, we have Professor Richardson, which
22 is the director of the Outcomes Center; he can provide

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1 an explanation for that.

2 But certainly at the time the idea was not
3 to come in to present and to compare a Harris Hip
4 Score. In fact, the scoring systems are very similar,
5 and from the perspective of the Oswestry Center what
6 was developed was better because it can be assessed by
7 the patient, and it's also validated.

8 If I could bring Professor Richardson to
9 talk about that, Dr. Naidu, or is that sufficient?

10 PANEL CHAIRPERSON NAIDU: I think we'll
11 just continue our deliberations at this point. Thank
12 you.

13 MR. VELEZ-DURAN: Thank you.

14 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
15 Kim.

16 Dr. Mabrey.

17 DR. MABREY: My answer has two parts to
18 it. Number one, I do think that ask the patient for a
19 self-evaluation is appropriate, and that is the way to
20 gather that data. So to specifically answer that
21 question, yes. I think that was appropriate.

22 However, I would like to add after seeing

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1 the presentations both in the FDA and from the sponsor
2 today, it appeared as though a tremendous effort was
3 brought forth in showing that the Oswestry was
4 equivalent to the Harris Hip Score. What I would have
5 liked to have seen or I think most investigators would
6 like to see would have been other scores by which to
7 judge that, and those are readily available, the SF-
8 12, the SF-36, the Womack from Canada, the Merle
9 D'Aubigne, which is popular in Europe.

10 It would have been nice to see some type
11 of parallel score to go with that. If there are plans
12 for further data collection, then I would certainly
13 put my suggestion in that some of those be included.

14 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
15 Mabrey.

16 Dr. Blumenstein.

17 DR. BLUMENSTEIN: I would answer that
18 there's adequate in the setting of an unmet medical
19 need, but in the setting of comparing to other
20 cohorts, there wasn't enough compatibility of
21 endpoints or schedule of assessments or other things
22 of that nature to allow even a cohort comparison.

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1 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
2 Blumenstein.

3 Dr. Mayor.

4 DR. MAYOR: I come from a hotbed of
5 patient centered evaluation instruments at the Center
6 for Clinical Studies at Dartmouth. So I have no
7 argument with the patient centered assessment
8 instruments that were used here, but I would suggest
9 that this Question 2 is very different from Question
10 1, and my response would cover not just Question 2 but
11 Question 3 as well.

12 While I have no argument that the methods
13 of evaluation used to collect effectiveness data in
14 the hands of Dr. McMinn and his operating skills
15 demonstrates the effectiveness of the device in that
16 context, I'm afraid I have no reassurance regarding
17 the applicability of that result to the experience
18 that we might generate when the approach is
19 generalized to the United States.

20 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
21 Mayor.

22 Mr. Melkerson, I'll summarize this

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1 question as follows. With regards to Question No. 2,
2 the panel in general believes that it is good to have
3 the outcome scores directly from the patient, but
4 nevertheless, the instruments of outcome used in this
5 study are not very adequate. It's not standard.
6 There have been references to SF-12, SF-36, Womack
7 scores referred to us by Dr. Mabrey, and in general,
8 it's good to have patient information rather than
9 surgeon evaluation, but nevertheless, the instruments
10 are lacking.

11 MR. MELKERSON: That's an adequate
12 response, but I would again ask: do you have any
13 comments for the same question?

14 PANEL CHAIRPERSON NAIDU: I would concur
15 with the panel with that.

16 Mr. Goode, would you mind posing Question
17 No. 3?

18 MR. GOODE: Question 3: please discuss
19 whether or not the foreign data from a single
20 investigator in U.K. practice of medicine is
21 applicable to the target U.S. population and practice
22 of medicine.

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1 PANEL CHAIRPERSON NAIDU: Let's start with
2 Dr. Mayor.

3 DR. MAYOR: Again, as I just finished
4 suggesting, it's not the issue of this being foreign
5 data or the issue of the question of whether the
6 citizens of the U.K. are a unique, strange or alien
7 population, but it is the work of a single unit and an
8 individual commission, and so I can't see within that
9 data any reassurance that it's applicable to the U.S.
10 population at risk.

11 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
12 Mayor.

13 Dr. Blumenstein.

14 DR. BLUMENSTEIN: My concern here is that
15 we have no estimate whatsoever of the variability
16 across surgeons or clinical sites. All we have is the
17 experience of the inventor.

18 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
19 Blumenstein.

20 Dr. Mabrey.

21 DR. MABREY: I concur with Drs. Mayor and
22 Blumenstein.

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1 PANEL CHAIRPERSON NAIDU: Dr. Kim.

2 DR. KIM: I also concur with the last
3 three panel members.

4 PANEL CHAIRPERSON NAIDU: Dr. Skinner.

5 DR. SKINNER: I'm afraid I'm going to
6 sound like an industry rep.

7 (Laughter.)

8 DR. SKINNER: If this study were going to
9 be done in a randomized controlled trial situation in
10 the United States, the company would go out and find
11 five excellent hip surgeons, and all of those hip
12 surgeons would be completely different from the
13 routine orthopedic surgeon who would do hip
14 replacements after it was approved.

15 The only difference I see between having
16 one surgeon do this and having the five or six or
17 eight other surgeons in the United States do it is you
18 only have one learning curve instead of six of them.

19 And I think that the population in the
20 U.K. is very similar to the population we would have
21 in the United States going to those six orthopedic
22 surgeons. It would be a referral practice of people

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1 going to get a particular procedure done by a
2 particular surgeon.

3 So I think that this data is perfectly
4 applicable to a target U.S. population.

5 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
6 Skinner.

7 Dr. Whittington.

8 MS. WHITTINGTON: I'm going to have to
9 agree with Dr. Skinner this time. I would agree that
10 it would be a referral practice, probably very, very
11 much like the population that Dr. McMinn's practice
12 is.

13 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
14 Whittington.

15 Ms. Adams.

16 MS. ADAMS: Well, it's clearly a weakness
17 that there's one investigator involved. I think
18 that's obvious. I'm not concerned about foreign data,
19 and then when you get to the single investigator
20 question I think the things that give me more comfort
21 is the data that the sponsor presented indicating
22 there were 140 surgeons who had conducted 3,374 cases.

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1 I think that's good information.

2 I think the extensive training plan that
3 they've presented is very comforting, and the last
4 piece that I'm comforted by is even though it may not
5 necessarily be required, the sponsor has already
6 offered to do an extensive post approval study, which
7 I think would be a source of additional information
8 that would be useful.

9 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
10 Adams.

11 Mr. Melkerson, with regards to Question
12 No. 3, again, the panel appears to be split, although
13 there is a majority opinion stating that experience
14 from a single surgeon from a large referral practice
15 would not be applicable to the U.S. population in
16 general.

17 And did you want my opinion?

18 (Laughter.)

19 MR. MELKERSON: Of course. See the
20 pattern?

21 PANEL CHAIRPERSON NAIDU: Yeah. I do have
22 to concur with Dr. Mayor, Dr. Blumenstein, Dr. Mabrey,

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1 and Dr. Kim. This would not be applicable to the
2 general practice of orthopedic surgery in the U.S.
3 population. This is a single surgeon study. That is
4 my opinion.

5 MR. MELKERSON: Thank you. That's an
6 adequate response.

7 PANEL CHAIRPERSON NAIDU: Let's move on to
8 Question No. 4. Mr. Goode, would you please post the
9 question?

10 MR. GOODE: Question 4: based upon the
11 safety data in the 2,385 patients in the overall
12 McMinn cohort, that is the data on revisions, adverse
13 events, and deaths, and the analysis of the metal ion
14 literature. Please discuss whether or not you believe
15 that the data contained in this PMA provide a
16 reasonable assurance of safety.

17 PANEL CHAIRPERSON NAIDU: Why don't we
18 start off with Dr. Mayor again?

19 DR. MAYOR: Given that no reassurance of
20 safety is going to be perfect, my response would be
21 that the data presented in this PMA provides a
22 reasonable assurance of safety.

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1 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
2 Mayor.

3 Dr. Blumenstein.

4 DR. BLUMENSTEIN: I concur that the data
5 shown on safety is adequate when referred to the
6 amount of efficacy demonstrated.

7 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
8 Blumenstein.

9 Dr. Mabrey.

10 DR. MABREY: I concur.

11 PANEL CHAIRPERSON NAIDU: Dr. Kim.

12 DR. KIM: I concur as well. Despite the
13 flaws in the methodology of obtaining the data, the
14 data is robust in number and significantly -- provides
15 a significant amount of data quantity to assure that
16 this device is likely safe.

17 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
18 Kim.

19 Dr. Skinner.

20 DR. SKINNER: I agree with Dr. Kim. I
21 think that the large number of patients, the lengthier
22 follow-up than would be done in a 100 total hip in one

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1 group, 100 total hip in the other group study for two
2 years that you see in this group is definitely enough
3 to show that it's reasonably safe.

4 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
5 Skinner.

6 Ms. Whittington.

7 MS. WHITTINGTON: I concur with Dr. Kim
8 and Dr. Skinner. I think the robustness of the data
9 that was presented is good.

10 PANEL CHAIRPERSON NAIDU: Ms. Adams.

11 MS. ADAMS: I agree.

12 PANEL CHAIRPERSON NAIDU: Thank you.

13 Mr. Melkerson, this is one of the few
14 questions where we have reached a unanimous okay. The
15 panel, in general, believes that this PMA does provide
16 a reasonable assurance of safety.

17 Did we address your concern adequately?

18 MR. MELKERSON: Yes, it did.

19 PANEL CHAIRPERSON NAIDU: Thank you.

20 MR. MELKERSON: But I'll give you the
21 opportunity if you want to put your two cents in.

22 PANEL CHAIRPERSON NAIDU: I do. I will

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1 echo the opinion of the panel. Thank you.

2 Mr. Goode, could we move on to Question
3 No. 5, please?

4 MR. GOODE: Question 5: based upon the
5 five-year survivorship analysis of the 1,626
6 procedures in the combined X-ray/Oswestry cohort, the
7 five-year radiographic data on the 124 procedures in
8 the X-ray cohort, the five-year pain and function
9 OSHIP data of the 1,111 unilateral procedures in the
10 X-ray/Oswestry combined cohort, and the five-year
11 patient satisfaction analysis^o of the 1,626 procedures
12 in the X-ray/Oswestry combined cohort., please discuss
13 whether or not you believe the data contained in this
14 PMA provide reasonable assurance of effectiveness.

15 PANEL CHAIRPERSON NAIDU: Thank you, Mr.
16 Goode.

17 Why don't we start with Ms. Adams?

18 MS. ADAMS: Well, I think the numbers are
19 pretty good. We're seeing things that are comparable
20 to -- they did a good job of comparing to other
21 devices, radiographic success, survivorship, adverse
22 events even. I think the numbers look very good. So

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1 I have no additional comments.

2 PANEL CHAIRPERSON NAIDU: Thank you.

3 Ms. Whittington.

4 MS. WHITTINGTON: I would concur with Ms.
5 Adams. I think the data supports it.

6 PANEL CHAIRPERSON NAIDU: Thank you.

7 Dr. Skinner.

8 DR. SKINNER: I think the data provides
9 reasonable assurance of effectiveness.

10 PANEL CHAIRPERSON NAIDU: Dr. Kim.

11 DR. KIM: I still have difficulty with
12 this question, although the robustness of the data,
13 the sheer numbers, makes me feel comfortable as to the
14 safety of this device. The methodology is
15 significantly flawed such that I cannot confidently
16 determine if this device is more or less effective
17 than the existing treatment that's available.

18 So I would say that it lacks enough
19 information to make that determination.

20 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
21 Kim.

22 Dr. Mabrey.

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1 DR. MABREY: If I could just make a
2 comment first. I also served as a reviewer for the
3 Journal of Arthroplasty, and I have to say that having
4 reviewed all of the data today and having seen all of
5 the presentations that being here today is like
6 reading one of the very best written papers for the
7 Journal of Arthroplasty. The only difference is that
8 the author is sitting right there and you can put him
9 on the spot at any time.

10 I think the data here is testament to the
11 skills, surgical skills and design skills, and I think
12 that it provides a reasonable assurance of the
13 effectiveness of this device, and that I feel that
14 it's similar to other devices that have already been
15 used widely throughout the rest of the world.

16 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
17 Mabrey.

18 Dr. Blumenstein.

19 DR. BLUMENSTEIN: Well, as I said in my
20 presentation, I think that there's adequate evidence
21 of efficacy against an unmet medical need, but where I
22 have a problem is whether this study fits the

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1 definition of a well controlled study in light of the
2 fact that there are predicate interventions in this
3 disease, and I don't think it serves the public well
4 when we can't compare the device under consideration
5 to the predicate devices.

6 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
7 Blumenstein.

8 Dr. Mayor.

9 DR. MAYOR: Well, my response may seem at
10 odds with what I've said earlier. I think bullet
11 points one, two, three, and four do provide reasonable
12 assurance of effectiveness even in the hands of a well
13 qualified and expert orthopedic surgeons in this
14 country and referral practices as is likely to be the
15 case with the application of this technique to those
16 individuals.

17 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
18 Mayor.

19 Mr. Melkerson, with regards to your
20 Question No. 5, it appears that the panel is in
21 general consensus that the device is effective,
22 although there are concerns raised again. The theme

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1 has been repetitive throughout all of the discussions.

2 The effectiveness apparently cannot be judged
3 adequately, namely, because of the single surgeon
4 experience and the retrospective analysis.

5 Have we addressed the question adequately?

6 MR. MELKERSON: Yes, you have, and also,
7 again, I'd like to ask your opinion as well.

8 PANEL CHAIRPERSON NAIDU: My opinion is
9 that the device is effective, but the data quality is
10 deficient.

11 Thank you.

12 Mr. Goode, would you mind going to
13 Question No. 6?

14 MR. GOODE: Question No. 6: do the
15 patients' selection methods and the data presented on
16 the BHR device support the proposed labeling
17 indication?

18 And also, please comment on any other
19 aspects of the product labeling, such as the
20 contraindications, warnings, precautions, potential
21 adverse effects on health.

22 PANEL CHAIRPERSON NAIDU: Again, Dr.

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1 Mayor, if you don't mind starting off the discussions
2 of this question for us.

3 DR. MAYOR: I think the contraindications
4 have been covered adequately as written. I think the
5 warnings related to patient selection and potential
6 adverse effects on health deserve extra emphasis in
7 regard to the expectation of future difficulties
8 handling metal ion release into the patient system
9 with particular emphasis on the possibility of
10 anticipated decline in kidney function.

11 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
12 Mayor.

13 Dr. Blumenstein?

14 DR. BLUMENSTEIN: No comment.

15 PANEL CHAIRPERSON NAIDU: Dr. Mabrey?

16 DR. MABREY: I agree with Dr. Mayor. I
17 think that the contraindications have been well
18 covered. I don't think there's anything else you can
19 do about warning people against the fact that their
20 femoral neck may fracture other than to advise and to
21 pick a very good surgeon, and I think the precautions
22 are appropriate.

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1 Most of the precautions and warnings tend
2 to apply to that of metal ions, and this is a more
3 general discussion. I would defer to Ms. Adams in
4 terms of where the warnings and contraindications have
5 gone with respect to other metal-on-metal devices
6 within the FDA.

7 But at this point I would agree that
8 they've been well identified.

9 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
10 Mabrey.

11 Dr. Kim.

12 DR. KIM: I would agree with Drs. Mayor
13 and Mabrey, and make a special emphasis that if it's
14 not already in the labeling insert, indicate that we
15 do not know what the relationship between metal ions
16 and adverse health is at the moment.

17 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
18 Kim.

19 Dr. Skinner.

20 DR. SKINNER: I agree with the previous
21 panel members except Dr. Blumenstein.

22 (Laughter.)

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1 DR. BLUMENSTEIN: I said no comment.

2 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
3 Skinner.

4 Ms. Whittington.

5 MS. WHITTINGTON: I would agree with the
6 other panel members, I guess, except Dr. Blumenstein
7 as well, and ask that because you have a distinct and
8 separate section for patient labeling that that
9 section really be screened and effective for the
10 patient to read and not for a physician to read to the
11 patient because that never happens.

12 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
13 Whittington.

14 Ms. Adams.

15 MS. ADAMS: I agree with Dr. Kim's
16 comments, as well as Ms. Whittington's.

17 I have two other comments. One is I'd
18 like to say that I think the sponsor did a pretty good
19 job handling the fact that they had to parse their way
20 through the patient selection methods by one
21 investigator and come up with a proposed labeling
22 indications. I think they did a pretty good job.

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1 The other thing that I would just like to
2 remind the sponsor is that we did make comments
3 previously about some other considerations that should
4 be made with FDA having to do with other items, such
5 as GFR, creatinine and that sort of thing, that should
6 be considered in the labeling.

7 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
8 Adams.

9 Mr. Melkerson, with regard to Question No.
10 6, the panel in general believes that the data
11 presented on the BHR device does support the proposed
12 labeling indication. There are some concerns,
13 however, with regard to metal ion release and renal
14 insufficiency in patient populations such as pre-
15 diabetes, hypertensive patients with renal failure.
16 Those things have to be obviously refined.

17 Did we adequately address your concerns?

18 MR. MELKERSON: Yes, you did. And again,
19 I would like your endeavor to give us your opinion as
20 well.

21 PANEL CHAIRPERSON NAIDU: My opinion is
22 similar to the panel's conclusion. Thank you.

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1 Mr. Goode, let's move on to Question No.
2 7.

3 MR. GOODE: Question 7: a reasonable
4 assurance of safety and effectiveness as defined in
5 Questions No. 4 and 5 above must be demonstrated for
6 device approval. If you believe the data in this PMA
7 demonstrate a reasonable assurance of safety and
8 effectiveness but think that there are remaining
9 specific questions regarding this device that should
10 be addressed in a post approval study, please identify
11 those questions.

12 PANEL CHAIRPERSON NAIDU: Thank you, Mr.
13 Goode.

14 This is a loaded question. I'd like Dr.
15 Mayor to start off again, please.

16 DR. MAYOR: I would urge a five and ten-
17 year interval of post market approval supervision if
18 this device is approved for release in the United
19 States, with specific attention to femoral side
20 complications, including subsidence of the femoral
21 component on the femoral head, and surveillance to
22 detect the effect of particulates and bioreactivity in

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1 the region of the hip joint itself.

2 I would also urge the establishment of a
3 five-year follow up for the cadre of patients treated
4 by the instructor group described by Dr. Rogerson.

5 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
6 Mayor.

7 Dr. Blumenstein.

8 DR. BLUMENSTEIN: I think the study as
9 proposed would be just another example of a poorly
10 controlled study, and it would pollute the literature,
11 and I would not be recommending such a thing be done
12 as a post approval study.

13 I think that if a post approval study is
14 done that it should be well controlled and
15 specifically a randomized clinical trial providing
16 adequate data with respect to other predicate devices.

17 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
18 Blumenstein.

19 Dr. Mabrey.

20 DR. MABREY: This particular device does
21 have the potential of failure at a much later time, as
22 patient's age, become more osteoporotic. So I concur

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1 with Dr. Mayor that a longer period of time directed
2 follow-up be applied.

3 I'd be interested to see what happens to
4 these people at ten years as they age to see if
5 there's any stress shielding around the stem, but I do
6 appreciate the sponsor's offering of a post market
7 approval study.

8 I do think that there's an opportunity
9 here, especially at the champion surgeons' sites to
10 initiate some controlled studies if that's possible,
11 and I want to encourage that.

12 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
13 Mabrey.

14 Dr. Kim.

15 DR. KIM: If this device is approved, I
16 would strongly recommend some conditions. I have two
17 concerns. The first is to identify if there are any
18 major learning curve problems. In other words, if we
19 have 100 surgeons during the first five procedures,
20 that's 500 procedures. I think that's enough to
21 identify a significant learning curve problem.

22 Therefore, I would recommend that one of

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1 the conditions be that it's released to a limited
2 number of people/centers, and that the surveillance is
3 on the order of a clinical trial. Of course, a
4 randomized controlled clinical trial would be optimal,
5 but if it is a longitudinal prospective study only,
6 that protocol should be agreed upon with the FDA to
7 include all of the inclusion/exclusion criteria, the
8 criteria for revision, a standardized follow-up
9 protocol along with agreed upon measures of success.

10 I can just go on and on, but just suffice
11 it to say a well designed study for a period of some
12 time.

13 And one final thing. On Slide 38, the
14 conditions of approval, the sponsor recommended 150
15 patients at up to 15 sites. That doesn't seem like a
16 lot of patients, but one cannot create that number
17 until you do a power analysis. So that number should
18 be revisited as well.

19 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
20 Kim.

21 Dr. Skinner.

22 DR. SKINNER: Well, I think Dr. Kim's

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1 suggestion of looking into the learning curve is
2 interesting, but I think we can almost guarantee there
3 will be a learning curve. It's just a matter of how
4 bad it's going to be.

5 But I think Dr. Blumenstein really has the
6 right answer here. I think a post marketing study of
7 any significance, of any size that would be
8 significant to get a randomized controlled trial would
9 simply be another PMA type of thing, and I don't think
10 that's the information we want.

11 That information won't come down the line
12 until five years, ten years later. I think if we were
13 going to request the company to spend that money, we
14 should ask them to take Dr. McMinn's first 200
15 patients and follow them for another five years and
16 see what happens to those patients as more information
17 sooner about the long-term effects of this prosthesis.

18 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
19 Skinner.

20 Ms. Whittington.

21 MS. WHITTINGTON: I think that there
22 definitely needs to be a post market approval process

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1 and it definitely needs to be well controlled, but I
2 also agree that taking the initial patients from Dr.
3 McMinn's patient population and tracking them along
4 with those same criteria that are defined in this well
5 controlled post market approval survey that's done,
6 with special attention to addressing those adverse
7 events and identifying the criteria so we have a
8 better handle on them, I think that's what I have the
9 least faith in what we've seen today, is how that was
10 collected and how it was defined and identified. So
11 that goes along with a well controlled study.

12 I also think a limited number of
13 practitioners may be a prudent thing to do, given the
14 difference in the technique with this procedure versus
15 some of the techniques that we currently are using.

16 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
17 Whittington.

18 Ms. Adams.

19 MS. ADAMS: I do believe that the data in
20 the PMA demonstrated a reasonable assurance of safety
21 and effectiveness.

22 I agree with Dr. Skinner that there would

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1 be real value in following some of the earlier
2 patients out to later dates. I disagree with Dr. Kim
3 that 150 patients in a randomized controlled trial
4 will provide significantly more or different
5 information than we have today. I think that's
6 unlikely.

7 I also think, even though I don't
8 typically design clinical trials myself, that having
9 this device on the market and people being interested
10 in coming and asking for it provides some real
11 problems to the sponsor in terms of randomizing and
12 how the clinical trial is handled.

13 And finally, I'd like to suggest that the
14 sponsor and FDA take into account our own comments
15 here today and work up a post approval study that
16 would address them in the most effective way.

17 PANEL CHAIRPERSON NAIDU: Thank you, Ms.
18 Adams.

19 Mr. Melkerson, the answer to this question
20 is all over as you have heard. There is a general
21 consensus that the panel in general wants a fairly
22 extensive post market surveillance study. It appears

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1 that we're back to randomized controlled trials, and
2 it appears that the panel does not believe that there
3 is a reasonable appearance that based on this
4 submission, this data alone, we can answer this
5 question adequately.

6 Does that generally answer?

7 MR. MELKERSON: Just for clarification,
8 can you go over again the specific questions? I heard
9 long term.

10 PANEL CHAIRPERSON NAIDU: Yes. Dr. Mayor
11 suggested five to ten-year post market approval study
12 including surveillance, all femoral components, five-
13 year follow-up of metal ion release.

14 Dr. Kim suggested additional randomized
15 controlled trials of 150 patients.

16 Dr. Mabrey thought that post market
17 approval would be appropriate.

18 Dr. Blumenstein plainly said, "No need for
19 that. Just do a randomized controlled trial."

20 Dr. Skinner went on to say that it would
21 be nice to follow 200 initial patients of Dr. McMinn.

22 DR. SKINNER: But not do a randomized

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1 controlled trial.

2 PANEL CHAIRPERSON NAIDU: Not do. Okay.

3 DR. SKINNER: Because we'd be getting the
4 data from five years out already. That would be
5 interesting data. If we do a randomized controlled
6 trial, we don't have that data for five more years,
7 even the five-year data.

8 So I think that randomized controlled
9 trial is a waste of money, to be honest.

10 PANEL CHAIRPERSON NAIDU: Okay. Ms.
11 Whittington wished to have a more controlled PMA.

12 And the only one with full support is Ms.
13 Adams.

14 Yes, Dr. Kim.

15 DR. KIM: Point of clarification. The
16 number for 150 that was mentioned, that's the number
17 that the sponsor had proposed. My point was that that
18 150 number is a number that has no basis and that we
19 need to identify what that proper number is if we're
20 going to do a post market surveillance study.

21 It could be more than 150. It could be
22 less or it could be 150, but that number was derived

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1 without any basis. I just wanted to make that
2 clarification.

3 MS. ADAMS: May I make a comment?

4 PANEL CHAIRPERSON NAIDU: Yes.

5 MS. ADAMS: There is a basis, and as we
6 talked about before, these types of devices are
7 typically studied in 150 to 200 patients with two-
8 year follow-up. So typically that is what you would
9 see.

10 What we have here is something far in
11 advance of that already, and we're asking the sponsor
12 to go on and do that in addition. So I think we ought
13 to keep that in mind.

14 MR. MELKERSON: I think that answers our
15 question, but again I would like to ask your opinion
16 on this.

17 PANEL CHAIRPERSON NAIDU: Yes. My opinion
18 is that I think there is a reasonable assurance for
19 safety and effectiveness in this PMA that's presented
20 based on the single surgeon experience retrospective
21 of you, but as the other panel members have already
22 cited, post market study is important with regards to

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1 metal ion release, failure of devices, and Dr.
2 Skinner's suggestion of following 200 patients from
3 the initial quote of Dr. McMinn would be a valuable
4 addition to the study.

5 Have we addressed all of the panel
6 questions adequately, Mr. Melkerson?

7 MR. MELKERSON: I believe so.

8 PANEL CHAIRPERSON NAIDU: At this time
9 we'll adjourn the meeting -- well, not quite. We'll
10 take a break.

11 (Laughter.)

12 PANEL CHAIRPERSON NAIDU: Let's take a
13 short break and we'll come back.

14 (Whereupon, the foregoing matter went off
15 the record at 3:26 p.m. and went back on
16 the record at 3:40 p.m.)

17 PANEL CHAIRPERSON NAIDU: Now that the
18 panel has responded to the questions, we will open our
19 second open public session. Does anyone here wish to
20 address the panel now? If so, please come forward to
21 the podium and state your name, affiliation and
22 indicate your financial interest, if any, in the

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1 device being discussed today or any other device.

2 MR. THOMAS: Hello. My name is Craig
3 Thomas. I'm an orthopedic surgeon in Washington, D.C.

4 I have no financial interest in this
5 device or Smith & Nephew. I'll just give you a brief
6 history of my background and why I have an interest in
7 this hearing.

8 I did my residence in orthopedic surgery
9 and did a fellowship with Michael Mont (phonetic) at
10 Sinai Hospital in Baltimore, Maryland. For that
11 reason I have about one year and six months experience
12 clinically with metal-metal resurfacing, not
13 specifically this device.

14 I just have some answers to some of the
15 questions that panel had that were not provided or
16 were not as clear and so I just want to address them.

17 The first one was learning curve, surgical technique;
18 what is the learning curve; are there any studies?
19 Is there any data that we have to offer?

20 Well, at this year's academy meeting for
21 orthopedic surgery, I believe it was Poster 410.
22 Michael Mont and myself presented a paper that

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1 addressed the learning curve of resurfacing
2 arthroplasty.

3 One of the papers, there was a three-year
4 follow-up, and just to summarize it briefly, with our
5 first 50 patients, we had 11 femoral neck fractures,
6 which was significant. The second 50, we had one.
7 Then after that 100, from one to 200 we had a zero
8 fracture rate.

9 So there is a learning curve, but we
10 learned from our learning curve, and we've learned how
11 to avoid that, and I think that as different companies
12 educate different surgeons how to do the procedure
13 that you won't have what we had in the first 50. And
14 this is in the United States in Baltimore.

15 So to address that I can't predict what
16 it's going to be, but there is a learning curve, and I
17 think we can make it better.

18 The other thing that some folks had a
19 concern about was a limp. That's hard to contribute
20 to this actual implant device. Most total hip
21 patients will have a limp, both preop and postop, and
22 it does go away, and sometimes it doesn't, and that's

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1 dependent on several factors.

2 You had a limp before surgery. The
3 surgical approach that was used, the type of repair
4 that was used, the patient's motivation, the physical
5 therapist. It has a number of factors, and also at
6 this year's academy we presented a paper that showed
7 that a -- a gait analysis paper with resurfacing
8 patients compared to standard total hip patients --
9 that showed that the resurfacing patients had a near
10 normal gait pattern, and this was evaluated in a gait
11 lab at the Rubin Institute for Advanced Orthopedics.

12 Again, I believe it's poster 410. I'm not
13 sure of the other one, but you can look up Mont, et
14 al. We had a total of 18 presentations at the
15 academy, and it would be in one of those on the
16 academy web site.

17 Let's see. There was a question, I
18 believe, in reference to why not patients who are
19 older than 70, and I think that's a good question, and
20 it's going to be surgeon-patient dependent based on
21 the integrity of your bone structure whether or not it
22 would be offered. And I think it would be a mistake

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1 to put an age limit on that number.

2 Let's see. The next point. Someone asked
3 about incision size because there is sort of I would
4 say patient and industry driven desire to have smaller
5 incisions.

6 Well, also at this academy we presented a
7 paper on resurfacing in general where we took the size
8 of the incision from 11 centimeters to six centimeters
9 which is two and a half inches. So if you pull out
10 your car key -- now the car keys are bigger -- but the
11 standard house key and make that one and a half,
12 that's about two and a half inches. That's a fairly
13 small incision, and this is for a hip resurfacing.

14 I do agree that this is not something that
15 we start out training folks how to do minimally
16 invasive resurfacing arthroplasty, but it can be done.

17 Patient labeling was a question that was
18 addressed about renal patients. Preoperative lab work
19 is obtained, and that identifies that. I think that
20 was appropriately addressed.

21 The other question was about avascular
22 necrosis and size, size of the lesion, and

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1 contraindications. I think that that should be a
2 discussion that's left between the patient and doctor
3 as we review radiographs and MRIs and talk about
4 whether or not you're a candidate for it.

5 And actually what we did at the Rubin
6 Institute is a lot of times that's an intraoperative
7 decision. The patient understood that if we
8 interoperatively could not or did not feel confident
9 putting a femoral head resurfacing on that they would
10 be converted to a total hip replacement, and I think
11 that that should be preserved.

12 Let's see. The one thing that is sort of
13 bothersome to me, but I understand, is the analysis of
14 some of the data here. In my opinion we're being very
15 critical of some of the data. I could take any one of
16 the members of this panel tomorrow if you meet the
17 preoperative criteria and give you both components
18 separately.

19 So the acetabular component, I can use
20 that part as a total hip replacement, as an FDA
21 approved device. The femoral component, I can cap
22 your femoral head as an FDA approved device. I just

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1 can't put the two together.

2 And when you put the two together, you
3 have the metal-on-metal articulation, which I do that
4 already, but with a stem. So now I'm taking the
5 femoral part, putting a stem on it. You still have
6 the metal-on-metal component, basically the same
7 component that you guys are looking at, with a stem.

8 So when you're talking about metal ions
9 and everything, everything that you're really focusing
10 on in a negative mode is the articular interaction,
11 but I could do that tomorrow FDA approved.

12 So if I can do that and if this does not
13 get approved, then you may want to strongly look at
14 what's already on the market and pulling it.

15 So I just wanted to address some of those
16 concerns. I would take any questions from anyone. I
17 was not prepared to even talk to you guys. I didn't
18 even know this was happening until this week. I
19 happened to have a dental appointment that I canceled
20 once I found out that this was here. So thank you for
21 that.

22 (Laughter.)

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1 DR. THOMAS: And I stayed longer and
2 longer, I just had more things that I thought should
3 be addressed or at least explained to you.

4 My patient population cannot afford to go
5 overseas and spend the 15, 20, \$35,000 that's required
6 to do this. I have a list of 55 patients that have
7 been waiting for this to be approved. About five of
8 them I've had to recently go ahead and give them a hip
9 replacement because it's affecting their life. The
10 pain that they're going through and the wait and the
11 wait and the wait.

12 So I just give you this information. Does
13 anybody have any questions for me? I will take any.

14 That's it.

15 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
16 Thomas.

17 Any questions from the panel?

18 DR. MAYOR: It's not exactly a question.
19 You may have missed the CBS Sunday Morning broadcast
20 last weekend. They had a feature from India, and
21 there was an Indian surgeon, who has been trained to
22 do this procedure, and the patient went from Vero

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1 Beach, Florida to India and back, spending about
2 \$6,000 total for the surgery, entire hospital stay,
3 and three weeks in a beach side resort about an hour
4 from the hospital.

5 DR. THOMAS: Maybe I'll go get my hip
6 done.

7 (Laughter.)

8 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
9 Thomas.

10 Is there any further comment or
11 clarification from the FDA? Mr. Goode?

12 MR. GOODE: No, sir.

13 PANEL CHAIRPERSON NAIDU: Thank you.

14 Is there any further comment or
15 clarification from the sponsor? Mr. Duran?

16 MR. VELEZ-DURAN: No, there's no
17 additional clarifications. We want to thank the panel
18 for your time and effort.

19 PANEL CHAIRPERSON NAIDU: Thank you.

20 We're now ready to vote on the panel's
21 recommendation to the FDA for this PMA. Ms. Scudiero
22 will now read the panel recommendation options for the

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1 PMA.

2 Ms. Scudiero.

3 MS. SCUDIERO: These are the panel
4 recommendation options for premarket approval
5 applications.

6 The Medical Device Amendments to the
7 Federal Food, Drug and Cosmetic Act, as amended by the
8 Safe Medical Devices Act of 1990, allows the Food and
9 Drug Administration to obtain a recommendation from an
10 expert advisory panel on designated medical device
11 premarket approvable applications that are filed with
12 the agency. The PMA must stand on its own merits, and
13 your recommendation must be supported by the safety
14 and effectiveness data in the application or by
15 applicable publicly available information.

16 Safety is defined in the act as reasonable
17 assurance based on valid scientific evidence that the
18 probable benefits to health under conditions of
19 intended use outweigh any probable risks.

20 Effectiveness is defined as reasonable
21 assurance that in a significant portion of the
22 population the use of the device for its intended uses

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1 and conditions of use when labeled will provide
2 clinically significant results.

3 Your recommendation options for the vote
4 are as follows:

5 One, approval if there are no conditions
6 attached.

7 Two, approvable with conditions. The
8 panel may recommend that the PMA be found approvable
9 subject to specified conditions, such as physician or
10 patient labeling, education, labeling changes, or
11 further analysis of existing data. Prior to voting
12 all of the conditions should be discussed by the
13 panel.

14 Three, nonapprovable. The panel may
15 recommend that the PMA is not approvable if the data
16 do not provide a reasonable assurance that the device
17 is safe or that the data do not provide a reasonable
18 assurance that the device is effective under the
19 conditions prescribed, recommended, or suggested in
20 the proposed labeling.

21 Following the voting the Chair will ask
22 each panel member to present a brief statement

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1 outlining the reasons for their vote.

2 PANEL CHAIRPERSON NAIDU: Are there any
3 questions from anyone on the panel about these voting
4 options before I ask for a main motion on the
5 approvability of this PMA? Dr. Mayor.

6 DR. MAYOR: A minor question related to
7 the last sentence in the preamble. Effectiveness is
8 defined as reasonable assurance that in a significant
9 proportion of the population use of this device for
10 its intended uses and conditions of use when labeled
11 will provide clinically significant result.

12 And I suggest that we really are looking
13 for more than just that, but a clinically significant
14 beneficial result.

15 MS. SCUDIERO: I believe that is what is
16 intended even though that is not stated. That's a
17 good comment.

18 DR. MAYOR: Okay.

19 PANEL CHAIRPERSON NAIDU: Thank you, Dr.
20 Mayor.

21 Is there a motion for either
22 approvability, approval with conditions or disapproval

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